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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,789	04/08/2005	Yutaka Tokiwa	SAEG 184.001APC	9374

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EXAMINER	
GOON, SCARLETT Y	

ART UNIT	PAPER NUMBER
4131	

NOTIFICATION DATE	DELIVERY MODE
04/02/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/530,789	TOKIWA ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	4131	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *3-8 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2,9 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-36* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 July 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a National Stage entry of PCT/JP03/13018 filed on 10 October 2003, and claims priority to Japanese patent application No. 2002-297040, filed on 10 October 2002, Japanese patent application no. 2002-353403, filed on 5 December 2002, Japanese patent application no. 2003-117973, filed on 23 April 2003, and Japanese patent application no. 2003-294543, filed on 18 August 2003. A certified copy of each foreign priority document, in Japanese, has been received.

Information Disclosure Statement

The information disclosure statement (IDS) dated 1 July 2005 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Election/Restrictions

Applicants' election without traverse of Group I, encompassing claims 1-17, drawn to an arbutin ester derivative and the process for producing said derivative, in the reply filed on 14 February 2008, is acknowledged. Claims 18-36 have been cancelled by applicants.

Applicants further elect, without traverse, the disclosed species of formula 2, encompassed by claim 2, wherein R_1 is a single bond. Applicants' species has been found free of the prior art and the search has been extended to include the species of formula 9, wherein R_1 is an alkylene group.

Claims 3-8 and 10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 14 February 2008.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites "an arbutin ester compound ... represented by formula (2) wherein R_1 is a single bond, an alkylene group or an arylene group." The metes and bounds of the claim are unclear. The applicants do not define what is meant by a single bond, an alkylene group or an arylene group within the specification. Generally, it is understood that a single bond connects two atoms and encompasses no other groups or atoms in between. Similarly, an alkylene group is a double bond connecting two carbon atoms. However, according to the specification, a compound of formula (2) encompasses a 10-undecylenic acid derivative as a side chain. An undecylenic acid group contains a ten carbon alkyl chain wherein the terminal carbon is an alkene. The undecylenic acid group is not encompassed by the meaning of a "single bond" or an

"alkylene group". Thus, it is unclear and indefinite as to the meaning of "a single bond, an alkylene group or an arylene group".

The recitation of "a tyrosinase inhibitor comprising" in claim 11 renders the claim herein indefinite. The use of the language "comprising" leaves the claim open for inclusion of unspecified components. However, a tyrosinase inhibitor is regarded as a single compound. As such, a compound cannot comprise additional components. Thus, this renders the claim unclear and indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 9, and 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakajima *et al*.

Nakajima *et al.* teaches the lipase-catalyzed synthesis of arbutin cinnamate in an organic solvent. As shown in figure 1 (see below and p. 1926), arbutin cinnamate was synthesized from arbutin and vinyl cinnamate by regioselective transesterification with a bacterial lipase in acetonitrile.

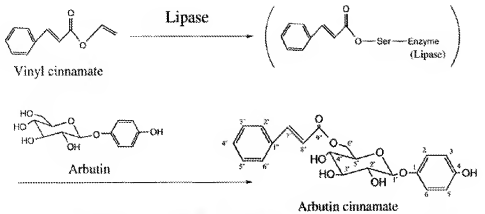

Fig. 1. Reaction Scheme for Lipase-catalyzed Regioselective Transesterification to Synthesize Arbutin Cinnamate

With respect to the art rejection above, it is noted that the reference does not teach that the compound can be used in the manner instantly claimed, as a tyrosinase inhibitor and as an external preparation for the skin comprising the tyrosinase inhibitor. However, the intended use of the claimed compound does not patentably distinguish the compound, per se, since such disclosed use is inherent in the referenced compound. In order to be limiting, the intended use must create a structural difference between the claimed compound and the prior art compound. In the instant case, the intended use does not create a structural difference, thus the intended use is not limiting.

The arbutin cinnamate compound disclosed by Nakajima *et al.*, as well as the reaction scheme describing the synthesis of the arbutin cinnamate, anticipates instant claims 1, 9, and 11-14.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Section [0001]

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nakajima *et al.*, as applied to claims 1, 9, and 11-14, and further in view of Lozano *et al.*

The teachings of Nakajima *et al.* were described in the above claim rejections under USC § 102. Nakajima *et al.* fails to teach a process for the esterification of the arbutin compound, wherein the esterification is carried out while performing a dehydration treatment. This deficiency is addressed by Lozano *et al.*

Lozano *et al.* teaches methods for the synthesis of butyryl esters from trimethylammonium alcohols in dry conditions catalyzed by immobilized *Candida Antarctica* lipase B. The synthetic activity of the enzyme is strictly dependent on the water content, the position of the hydroxyl group in the trimethylammonium molecule, and the log P parameter of the assayed solvent (p. 352, abstract). Therefore, anhydrous conditions and a high excess of the vinyl ester over L-carnitine is necessary (p. 352, abstract). Before the solvents and vinyl esters were used in the reaction, water was removed by adding molecular sieves to the reagents, and allowing the mixture to shake for 24 hours at room temperature (p. 353 under subheading "Drying of Chemicals and Water Content Analysis"). Towards setting up the synthetic reaction, 100 μmol of choline or L-carnitine and 100 mg of molecular sieves were placed in a screw-capped vial with a Teflon seal. Then, 1 mL of an appropriate mixture of dried vinyl ester and solvent was added. The resulting reaction was incubated with gentle shaking overnight at 40 °C to reach solubility equilibrium. The reaction was then initiated by the addition

of 20 mg of immobilized enzyme and the reaction was allowed to proceed at 40 °C with shaking.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Nakajima *et al.*, concerning the lipase-catalyzed synthesis of arbutin cinnamate in an organic solvent, with the teachings of Lozano *et al.*, regarding methods for the synthesis of butyryl esters from trimethylammonium alcohols in dry conditions. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Lozano *et al.*, that the synthetic activity of the lipase is strictly dependent on the water content, making it necessary to run the reaction under anhydrous conditions.

Absent of any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in synthesizing the arbutin cinnamate described by Nakajima *et al.*, using the anhydrous lipase-catalyzed conditions as described by Lozano *et al.*

Section [0002]

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nakajima *et al.*, as applied to claims 1, 9, and 11-14, and further in view of Japanese patent 2001-151623 to Kiyoshi *et al.* (machine translation).

The teachings of Nakajima *et al.* were described in the above claim rejections under USC § 102. Nakajima *et al.* fails to teach a process for the esterification of the

arbutin compound, wherein the esterification is carried out in the presence of a chemical catalyst. This deficiency is addressed by Kiyoshi *et al.*

Kiyoshi *et al.* teaches the preparation of a skin lotion obtained by formulating an acylated derivative of glycosyl-L-ascorbic acid with silicone oil. An acyl ester can be introduced onto glycosyl-L-ascorbic acid via a chemical reaction (p. 3, section 0009) or an enzymatic reaction (p. 4, section 0011). In the case of a chemical reaction, acylating agents that can be used include an acid or acid halide, an anhydride, or an acid ester (p. 3, section 0009). The reaction is generally performed to the exclusion of water, usually in organic solvents such as pyridine, dimethylsulfoxide, and dimethylformamide (p. 4, section 0010). The reaction proceeds regioselectively onto the 6-OH group of the glycosyl moiety. Upon completion of the reaction, the product can be purified by salting out, dialysis, filtration, concentration, fractional precipitation, liquid extraction, or chromatography (p. 5-6, section 0012). In their examples, Kiyoshi *et al.* describes the synthesis of 2-*O*-α-D-monoglucopyranosyl-6-*O*-octanoyl-L-ascorbic acid. First, 2-glucosylpyranosyl-L-ascorbic acid is dissolved in pyridine. Next, a solution of caprylic anhydride in pyridine is added to the glucosylpyranosyl-L-ascorbic acid solution and the reaction is allowed to proceed for 165 minutes at room temperature. The reaction is stopped by the addition of methanol.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Nakajima *et al.*, concerning the lipase-catalyzed synthesis of arbutin cinnamate in an organic solvent, with the teachings of Kiyoshi *et al.*, regarding the preparation of a skin lotion obtained by formulating an acylated derivative

of glycosyl-L-ascorbic acid with silicone oil. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Kiyoshi *et al.*, that the chemical reaction is complete in 165 minutes whereas an enzymatic reaction can proceed for days.

Absent of any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in synthesizing the arbutin cinnamate described by Nakajima *et al.*, using the chemical conditions as described by Kiyoshi *et al.*

Section [0003]

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nakajima *et al.*, as applied to claims 1, 9, and 11-14, and further in view of Japanese patent 2001-151623 to Kiyoshi *et al.* (machine translation) and published international application WO 01/79241 A1 by Weiss *et al.* (machine translation).

The teachings of Nakajima *et al.* were described in the above claim rejections under USC § 102. Nakajima *et al.* fails to teach a process for producing an arbutin ester, wherein the esterification reaction is followed by the steps of extraction and isolation to purify out the arbutin compound. This deficiency is addressed by Kiyoshi *et al.* and the '241 patent application by Weiss *et al.*

The teachings of Kiyoshi *et al.* were described above in section [0002] of the claim rejections under USC § 103. In particular, various methods for purification after

an esterification reaction were described (p. 5-6, section 0012). Kiyoshi *et al.* fails to provide details as to how the purification by liquid extraction is performed.

Weiss *et al.* teaches the production and use of glycoside esters in cosmetics, pharmaceutical products and foodstuff or animal feed. To purify the products in the esterification reaction, Weiss *et al.* teaches two methods. The first method involves an aqueous two-phase extraction procedure and the second method involves silica gel column chromatography (p. 4, paragraph 10; claim 17). In the aqueous two-phase extraction procedure with water, organic solvents such as n-hexane, cyclohexane, THF or diethylether may be used to separate the product from the non-reacted acid/esters.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Nakajima *et al.*, concerning the lipase-catalyzed synthesis of arbutin cinnamate in an organic solvent, with the teachings of Kiyoshi *et al.*, regarding the preparation of a skin lotion obtained by formulating an acylated derivative of glycosyl-L-ascorbic acid with silicone oil, with the teachings of Weiss *et al.*, regarding the production, purification, and use of glycoside esters in cosmetics, pharmaceutical products and foodstuff or animal feed.

As such, it would be *prima facie* obvious that a compound can be purified using the two-phase liquid extraction technique. A skilled artisan is well aware of the various methods that may be employed in the purification of a compound, and would therefore select the method that is most suitable for their purposes.

Absent of any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in purifying the

arbutin cinnamate described by Nakajima *et al.*, using the purification procedure as described by Weiss *et al.*

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Andres/

Supervisory Patent Examiner, Art Unit 4131

/S. G./
Examiner, Art Unit 4131